## REMARKS

The claims are 1-6. Claims 1-6 have been amended to correct obvious typographical errors and grammatical errors. Further, As such, the corrections are not new matter because the corrections are apparent from the examples and recitations elsewhere in the specification.

Rejections Under 35 USC §103

The claims have been rejected as allegedly being unpatentably obvious over U.S. Patent No. 5,998,437 ("Nishi") in combination with U.S. Patent No. 4,950,680 ("Taylor"), *J. Cellular Biochem.* Supp. 161:156-166 ("Earnest"), and *J. Biological Chem.* 272(23):14860-14866 ("Fang"). Applicants respectfully submit that a prima facie case has not been presented for obviousness in light of any of the cited references individually or in any combination.

To make a prima facie case for obviousness, each element of the rejected claim must be present in the cited references. Applicants respectfully submit that the references do not disclose, teach or motivate the use of the compounds in the present invention to treat precancerous lesions, to inhibit the growth of neoplastic cells, or to regulate apoptosis in human cells.

Nishi describes fused pyridine as inhibitors of cGMP-specific PDE (PDE V). Nishi does not suggest that such fused pyridine compounds might be used to treat precancerous lesions, to inhibit the growth of neoplastic cells, or to regulate apoptosis in human cells.

However, Fang does not demonstrate that such fused pyridine compounds might be used to treat precancerous lesions, to inhibit the growth of neoplastic cells, or to regulate apoptosis in human cells. Indeed, Fang first makes clear that ANP-induced apoptosis is myocyte-specific at page 14862. Next, Fang demonstrates that cGMP, mediated by guanylyl cyclase "may participate in ANP-induced apoptosis." Thus, the Examiner is making a leap to conclude that any cGMP-specific PDE inhibitor, such as the benzimidazole compounds used in the present invention, would treat precancerous lesions, inhibit the growth of neoplastic cells, or regulate apoptosis in human cells.

Similarly, Taylor does not disclose, teach or motivate that benzimidazoles can be used to treat precancerous lesions, to inhibit the growth of neoplastic cells, or to regulate apoptosis in human cells. Taylor very specifically describes a combination of two members from a prostacyclin, a calcium channel blocker, a thromboxane synthase inhibitor, and a phosphodiesterase inhibitor, to inhibit tumor cell induced platelet aggregation. Taylor makes it clear that such platelet aggregation is a surrogate for metastasis and that inhibition of such aggregation may be useful against metastasis (see, for example, col. 2, lines 10-23; col. 3, lines 43-46; col. 3, lines 60-65; col. 4, lines 20-24; col. 4, lines 28-31; col. 4, lines 44-45; col. 11, lines 40-55; and col. 18, lines 5-7. Indeed, Taylor states at col. 18, lines 5-7 that "[t]he use of the combinations of the claimed agents in vivo is expected to significantly inhibit tumor cell induced metastasis." Thus, Taylor does not disclose, teach or motivate one in the art to aminothiohene carboxylic acid amides– certainly not cGMP-specific PDE inhibitors – or indeed, any chemical class used alone, to treat neoplastic or precancerous lesions.

Earnest is directed to the use of NSAIDs, particularly piroxicam, which may be useful for the chemoprevention of colon cancer. In a section spanning pages 157-158, Earnest conjectures that NSAIDs may protect against cancer because NSAIDs have been noted to affect cell proliferation, inhibit rat hepatoma, and human fibroblast cells. Further, a specific NSAID, indomethacin, is described as arresting the progression of certain cell cycle and DNA synthesis. Finally, Earnest speculates that NSAIDs may affect carcinogenesis by modifying enzymes other than cyclooxygenase, citing phosphodiesterase and cyclic AMP protein kinase as possibly examples – both of which might be integral to cancer initiation and promotion. Thus, one in the art reading Earnest is only provided disclosure about the use of NSAIDs and how such compounds, together with a possible putative effect by NSAIDs on other enzymes, might be useful against cancer. There is no disclosure, teaching or motivation that the general class of any cGMP-specific PDE inhibitors, and certainly not the benzimidazole derivatives of the present invention, would be useful to treat precancerous lesions, to inhibit the growth of neoplastic cells, or to regulate apoptosis in human cells.

Applicants respectfully point out that the elements of the claims, as presently amended are not taught in the references in any combination. Applicants respectfully

submit that the Examiner has not met that burden to demonstrate prima facie obviousness. Indeed, prominently absent from the cited references is a definitive statement that cGMP-specific PDE inhibitors regardless of the inhibitors' chemical class would be expected to be useful to treat precancerous lesions or to inhibit the growth of neoplastic cells. One in the art is simple put at a lost to make the connection between the cited references and Applicant's invention except by impermissibly using the invention as a template.

Applicants respectfully submit that the Examiner is impermissibly using an obvious to try standard or impermissibly is using hindsight by using the invention as a template. Thus, Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants respectfully submit that the application is in condition for allowance, and respectfully request a Notice to that effect. Attorney for Applicants can be reached at the telephone number and address below. Commissioner is authorized to charge any deficiencies and credit any overpayment to OSI Pharmaceuticals, Inc. Deposit Account No. **502783**.

Very truly yours,

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date appearing below.

OSI PHARMACEUTICALS, Inc.

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January 27, 2004
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